# CLINICAL PROCEEDINGS

*of the*

## CHILDREN'S HOSPITAL

WASHINGTON, D. C.



*March 1954*

VOLUME X NUMBER 3

# on every count SUPERIOR

**Superior flavor**

Exceptionally pleasant tasting... leave no unpleasant after-taste... readily accepted without coaxing.

**Superior stability**

Require no refrigeration; no expiration date on labels. May be safely autoclaved with formula.

**Superior miscibility**

Disperse instantly in formula, fruit juice or water ... mix well with Pablum and other solid foods.

**Superior convenience**

In ready-to-use form . . . no mixing necessary. Calibrated dropper assures easy, accurate dosage. For young infants, drop directly into mouth or mix with other foods. For older infants, measure into a spoon.

## Superior vitamin supplements for infants

## POLY-VI-SOL

SIX ESSENTIAL VITAMINS FOR DROP DOSAGE

Each 0.6 cc. of Poly-Vi-Sol supplies:

| | |
|---|---|
| Vitamin A | 5000 units |
| Vitamin D | 1000 units |
| Ascorbic acid | 50 mg. |
| Thiamine | 1 mg. |
| Riboflavin | 0.8 mg. |
| Niacinamide | 6 mg. |

## TRI-VI-SOL

VITAMINS A, D AND C FOR DROP DOSAGE

Each 0.6 cc. of Tri-Vi-Sol supplies:

| | |
|---|---|
| Vitamin A | 5000 units |
| Vitamin D | 1000 units |
| Ascorbic acid | 50 mg. |

All vitamins are in synthetic, hypoallergenic form.
Available in 15 cc. and 50 cc. bottles, with calibrated droppers.

**MEAD JOHNSON & COMPANY**
Evansville, Indiana, U.S.A.

MEAD

MEAD, JOHNSON & COMPANY, Suite 419 Eig Building, 8641 Coleville Road, Silver Spring, Maryland. JU 9-1222

# CLINICAL PROCEEDINGS

## OF THE CHILDREN'S HOSPITAL

13th and W Streets, Washington 9, D. C.

Vol. X *March 1954* No. 3

## CONTENTS





PUBLISHED MONTHLY BY THE STAFF AND RESEARCH FOUNDATION OF THE CHILDREN'S HOSPITAL, WASHINGTON, D. C.

Cases are selected from the weekly conferences held each Sunday morning at 11:00 A.M., from the Clinico-pathological conferences held every other Tuesday afternoon at 1:00 P.M., and from the monthly Staff meeting.

This bulletin is printed for the benefit of the present and former members of the Attending and Resident Staffs, and the clinical clerks of Georgetown and George Washington Universities.

Subscription rate is $2.00 per year. Those interested make checks payable to "Clinical Proceedings Dept.," The Children's Hospital, Washington, D. C. Please notify on change of address.



Entered as second class matter November 21, 1946 at the post office at Washington, D. C., under the Act of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 538, Act of February 28, 1925, authorized January 17, 1947.

# WATERHOUSE-FRIDERICHSEN SYNDROME

## A Review of the Literature and a Report of Two Cases of Fulminating Meningococcic Septicemia

Pacita Pronove-Irreverre, M.D.

### INTRODUCTION

With the advent of the sulfa drugs followed by the antibiotics and by the adrenal-cortical hormones, together with a better understanding of the functions of the adrenal glands and the use of the eosinophile count as a guide to adrenal status[13] contributing thereby to better clinical recognition, plus the encouraging reports of survival and recovery in an otherwise invariably fatal disease, revived interest has been focused on cases of fulminating meningococcic septicemia.

### CASE REPORT NO. 1

This is the first case of recovery from a fulminating meningococcic septicemia observed in this hospital.

A five year old white male was admitted to Children's Hospital on January 25, 1953 in a state of shock with an extremely weak, rapid and barely perceptible pulse. He appeared pale, was dehydrated and comatose with half-opened eyes and was covered with a generalized, reddish-purple rash. Frequently he would scream as if in pain while simultaneously throwing out his upper and lower extremities.

The present illness started at midnight about 18 hours prior to admission when the child suddenly woke up screaming and complained of pain in his left ankle. The mother noted that the child felt hot to touch. The fever remained high and the child continually asked for water until seven hours prior to admission when he became delirious, extremely restless, and talked incoherently. About four hours prior to admission a few dark brown, reddish spots were noted on the left side of his neck. These spots progressively and rapidly increased in number and became generalized within half an hour. Bowel movements were regular and normal. A doctor who saw the child just before admission advised immediate hospitalization.

Physical examination revealed a well-developed and well-nourished white male child who appeared critically ill, comatose and in a state of shock as described above. Temperature was 104.4°F. The skin was covered with petechiae, some discrete and others confluent, of varying sizes and colors. There were bright red petechiae on the bulbar and palpebral conjunctivae, on the soft palate, posterior pharyngeal wall, and tonsils. The latter appeared hemorrhagic in spots. The neck showed a 3+ rigidity. The lungs were clear and the heart was normal except for tachycardia. Brudzinzki and Kernig signs were both positive. The remainder of the physical examination was non-contributory.

The past history revealed a premature delivery by forceps after eight months of gestation and a birth weight of five pounds, four ounces. Development was normal. He received all routine immunizations and had no previous hospitalizations or childhood diseases.

The family history was non-contributory.

Immediately upon admission the child was put in an oxygen tent. Therapy was promptly instituted as follows:

1. Intravenous fluids: five per cent glucose in water, normal saline, and five per cent glucose in Hartman's solution were used and continued for 48 hours by the continuous drip method.
2. Blood transfusion of 300 cc. after partial hydration.
3. Antibiotics:
   A. Aureomycin—300 mgm. initial dose and then 200 mgm. every six hours in five per cent glucose and water I.V. for 48 hours. This was followed by aureomycin in a dose of 200 mgms. every four hours orally for the next 7 days.
   B. Penicillin—one million units of aqueous crystalline penicillin every two hours, I.M. for the first two and a half days. This was reduced to 500,000 units every four hours for the next seven days until one day before his hospital discharge.
4. Sodium sulfadiazine—one gm. every six hours in normal saline I.V. for the first 48 hours and followed by an equal dose given every four hours, orally for the next five and a half days for a total of seven and a half days.
5. Cortisone—50 mgm. I.V. and 50 mgm. I.M. were given simultaneously within an hour after admission and then 25 mgm. every twelve hours I.M. for two doses followed by 25 mgm. every twelve hours orally for the next three doses, that is, a total of 225 mgm. cortisone within three and a half days.
6. Oxygen—continuously for the first 48 hours.

Blood pressure readings were taken continuously from the time of admission. It took about ten minutes of repeated readings before the blood pressure registered feebly at about 40 systolic with unobtainable diastolic. The blood pressure was therefore presumed to be zero initially. In about another five minutes the blood pressure read 76/40. The pulse was still weak but slightly improved. Subsequent blood pressure readings taken about every fifteen minutes for the next 12 hours were more or less stabilized at 80/50 and this gradually improved to 100/70 on the third hospital day. At this level it remained stationary until discharge on the twelfth hospital day. Similarly the pulse improved in character.

An eosinophile count was taken on admission before the administration of cortisone and repeated every two hours after cortisone until two consecutive zero counts were obtained. Counts were then taken daily for the next two days during cortisone administration and repeated every two days until discharge. A Thorn test was done prior to discharge and found to be normal.

Blood chemistry determinations done daily for four consecutive days from admission included BUN, sugar, chlorides, $CO_2$ combining power and potassium. Sodium, unfortunately, was not determined because of inadequate blood samples withdrawn. Results are shown in table 1.

TABLE 1

*Blood Chemistries in Case #1*

| DAYS | K (MEG) | CL (MEG) | SUGAR (MGM%) | BUN | $CO_2$ VOL. % |
|---|---|---|---|---|---|
| 1 | 3.56 | 117 | 115 | 14.5 | 33 |
| 2 | 3.7 | 113 | 70 | 12.5 | 33 |
| 3 | 3.7 | 112 | 85 | 13.7 | 35 |
| 4 | 3.56 | 115 | 90 | 9.7 | 45 |

A peripheral blood smear on admission revealed toxic granulations of the neutrophiles and a blood count showed moderate leucocytosis which increased within the next two days and gradually dropped to normal on the seventh hospital day. Together with the leucocytosis there was a simultaneous shift to the left. The hemoglobin, red blood cell and hematocrit examinations, done three to five times were more or less within normal limits. Platelets grossly appeared normal. Results are shown in table 2.

TABLE 2

*Laboratory Study in Case # 1*

| DAYS | HGB | WBC | VPC | URINALYSIS |
|---|---|---|---|---|
| | *gm.* | | | |
| 1 | 11 | 17.1 | 37% | |
| 3 | 11 | 22.1 | 34% | Trace acetone |
| 4 | | | | 2-3 WBC |
| 6 | 12.1 | 16.6 | | 2-5 WBC (2+ acetone 10 mg% alb) |
| 9 | 12.1 | 10.2 | | Sulfa crystals |
| 11 | 10.6 | 9.6 | | 3-5 WBC |
| 12 | | | 39% | |

Blood culture—positive Neisseria intracellularis.

The blood culture was positive for *Neisseria intracellularis* on admission but was negative in a subsequent examination done the following day. The nose and throat culture done on admission both revealed Micrococcus pyogenes aureus.

The spinal fluid was examined daily from the day of admission prior to antibiotic therapy until the results were normal and then repeated on the day of discharge. The spinal fluid cell count showed a marked increase 12 hours after admission but gradually dropped to normal by the day of discharge. The polymorphonuclear leucocytes predominated during the acute phase of the disease. The protein was normal and the sugar moderately decreased. Both smear and culture were never found to be positive for any organism in all seven examinations done.

Urinalyses were all within normal limits, except for a two plus acetone and 10 mgm. per cent albumin on one occasion and the presence of sulfa crystals after seven days of treatment. The sulfa crystals disappeared the next day, when the drug was discontinued. Results are shown in table 2.

An electrocardiogram, taken three times on the second, third and fourth hospital days, respectively, revealed a vertical heart, a tendency to right axis deviation and a slightly prolonged PR interval which was at the upper limit of normal.

Eight hours after admission and after institution of treatment, the child was afebrile and the temperature dropped from 104.4°F. to 99°F. Except for a slight rise to 100°F. at the end of the first 24 hours, the temperature remained normal until discharge on the twelfth hospital day. Sixteen hours after admission the child was rational, alert, conscious of his surroundings and had improved remarkably. Forty-eight hours after admission the rigidity of the neck was minimal although both Brudzinski and Kernig signs were still 2+. The petechiae had become necrotic and pustular in some places. Three days after admission the petechiae in the conjunctivae and buccal mucosa had diminished in number and size. Brudzinski was negative

and Kernig only 1+. On the fourth hospital day the eyes and mouth were almost completely cleared of petechiae and the skin had cleared on the abdomen and back. On the sixth hospital day the skin was almost completely clear of petechiae.

A follow-up of the case in the Neurological Clinic one week after discharge showed a normal child with no complaints. One and a half months later, hearing seemed slightly diminished; however a tuning fork test revealed normal hearing. An electroencephalogram done a few days later revealed a mildly abnormal pattern without focus. Subsequent examination four months after discharge revealed a much improved child without complaints. Six months after discharge he was still doing fine except for a repeat complaint of slightly impaired hearing, which seemed to be of the conduction type.

## CASE REPORT NO. 2

A six year old colored female was admitted to Children's Hospital at midnight on January 30, 1953, convulsing and looking acutely ill with a temperature of 106.4°F.

This child had had a cold and slight cough for two weeks prior to admission for which she was seen at the Out Patient Department where a penicillin injection was given. A few days before admission the child developed a slight fever which suddenly rose on the night of admission. A generalized convulsion which lasted for about twenty to thirty minutes occurred. The child became limp after the convulsions. She was immediately brought to Children's Hospital.

The past history was non-contributory and the family history irrelevant.

On physical examination, the child was noted to be a well-developed and well-nourished colored female who looked actuely ill, respirations were rapid and regular, temperature was 106.4°F., pulse 150 per minute. Physical findings included a hot and dry skin without rashes, a supple neck with palpable and moderately enlarged cervical lymph nodes, an injected pharynx, enlarged injected tonsils without exudate, pale buccal mucosa, clear and resonant lungs, a rapid heart rate, a negative Brudzinski and Kernig, and diminished deep tendon reflexes.

Immediately after admission, antipyretics were administered and sodium luminal was given I.M. The child was then put in an oxygen tent. The blood count revealed toxic granulations and intracellular Gram negative Diplococci were seen in the polymorphonuclears. The child was immediately isolated and treated as a meningococcemia. The child suddenly and progressively developed petechiae which quickly covered her entire body and within a period of one half hour she was covered with small and large purpuric and ecchymotic areas. A rapid physical check revealed petechial and ecchymotic hemorrhages into the palpebral conjunctivae, soft palate, face, upper and lower extremities and the trunk. The child was delirious, talking incoherently and had moments of excitement when she would scream and thrash her extremities all at the same time. Temperature was still 106°F., pulse 156/min. and respirations 62/min. and regular. The neck had 2+ rigidity, the pharynx was moderately injected, the breath sounds harsh, the heart normal except for the tachycardia, the liver edge palpable, the spleen not palpable and Kernig and Brudzinski signs were negative.

Therapy was immediately instituted as follows:

1. Intravenous aureomycin—200 mgm.
2. Intravenous sodium sulfadiazine—1 gm.
3. Cortisone—(intravenously—50 mgms and intramuscularly—50 mgms.) These were given simultaneously.
4. Aqueous crystalline penicillin—1 million units every two hours for 2 doses.

5. 800 cc. 5 per cent glucose in water.
6. 200 cc. normal saline.
7. 300 cc. whole blood.

The initial blood pressure was 86/40 but this suddenly dropped to zero. The child went into shock with an extremely feeble and imperceptible pulse from which she never recovered in spite of therapy. She died seven hours after admission or about twelve hours after the sudden onset of the hyperpyrexia.

An eosinophile count before the administration of cortisone was 40/mm which dropped to zero when the count was repeated one and a half hours after cortisone. The spinal fluid was clear with only 5 white blood cells, 13 mgm. per cent protein and 54 mgm. per cent sugar. The smear and culture were both negative. The blood culture was positive for Neisseria intracellularis. The throat culture was positive for both B-hemolytic streptococcus and Neisseria intracellularis. The blood smear revealed the presence of toxic granulations and intracellular Gram negative Diplococci in the polymorphonuclear white cells. The WBC was 7,400 with a moderate shift to the left (67 per cent). No urinalysis was done because of anuria.

The autopsy findings included massive bilateral adrenal hemorrhages with degeneration and necrosis of the remaining cellular structure but with intact capsules. There was pulmonary congestion with intra-alveolar hemorrhage and focal hemorrhages in the right, middle and lower lobes. Petechiae were found on the cerebellar and pleural surfaces, gastric mucosa, serosa and mucosa of the small intestines and on the subcapsular surfaces of the kidneys. There was marked congestion of the laryngeal, tracheal and bronchial mucosa and of the spleen and kidneys. A small amount of xanthochromic fluid was seen in the peritoneal cavity.

## HISTORY

While Voelker[38] in 1894 was the first to describe an "acute specific fever" associated with peripheral vascular failure, purpura and hemorrhage into the adrenals, it was not until 1901 when Graham Little[23] first recognized and established the syndrome as a distinct clinical entity. Little reviewed nine hitherto unclassified cases and reported four of his own. Of the nine cases he reviewed, two had no purpura but were otherwise clinically and pathologically indistinguishable from the rest. Waterhouse[39] in 1911 first reviewed the literature and reported one case of his own. He found 15 reports of similar cases which revealed bilateral adrenal hemorrhages at autopsy and which were associated clinically with a sudden onset, a hemorrhagic rash (in 12), vomiting (in 6), diarrhea (in 5), convulsions (in 5), abdominal pain (in 3), a temperature range of 100°F. to 108°F. and followed by death within 24–48 hours (in 11). Again in 1918, Friderichsen[14] brought the literature up to date with the complete clinico-pathological picture. He reviewed a total of 28 cases and reported 2 of his own. It was not until 1933 that Glanzmann[15] named the syndrome after Waterhouse and Friderichsen. The original criteria for the Waterhouse-Friderichsen syndrome therefore, are a sudden onset of a fulminating septicemia associated with peripheral vascular collapse and purpura and followed by death within 24 to 48 hours, plus the finding of bilateral adrenal hemor-

rhages at autopsy. It is obviously a pathological diagnosis. Some of the synonyms used in the literature are acute hemorrhagic adrenalitis, suprarenal apoplexy[39] and purpura fulminans[30].

## Clinico-Pathological Variations

A review of the literature revealed a number of clinico-pathological variations which have been observed by various investigators since the syndrome was established as follows:

1. *Clinical Waterhouse-Friderichsen Syndrome without Adrenal Hemmorrhage:* In 1942, Williams[41] found seventeen cases of fulminating meningococcic septicemia indistinguishable from each other, but of which only nine had hemorrhage into the adrenals and eight without. Also, in 1948, Daniels[10] in a review of three hundred autopsies of meningococcic infections among army personnel found normal adrenals in four cases in whom the clinical course resembled that of the syndrome.

2. *Clinical Waterhouse-Friderichsen Syndrome with Adreno-Cortical Degenerative Changes without Hemorrhage:* In 1943, Banks and McCartney[5] found marked adrenal edema and focal inflammation or focal adrenalitis without hemorrhage, and in 1944, Rich[32] described instances of tubular degeneration without hemorrhage in cases which had the clinical picture of the syndrome. Again, in 1946, Kinsman, D'Alonzo and Russi[20] found two types of adrenal changes in five fatal cases, one a "degenerating, early and probably a reversible phase" and the other a "hemorrhagic and most likely terminal or irreversible phase." These they believe are stages in the same process.

3. *Clinical Waterhouse-Friderichsen Syndrome with Unilateral Adrenal Hemorrhage:* This has an incidence of 5 per cent according to Rucks and Hobson[33]. That the right adrenal gland usually is more frequently and more extensively involved than the left is probably due to two anatomical considerations according to Rabinowitz[31], namely, that the direct opening or the right adrenal vein into the inferior vena cava subjects the right adrenal easily to venostasis and that its location subjects it more readily to compression between the liver and the spine. Batten[4] in 1898, Aegerter[1] in 1936 and Bush and Bailey[7] in 1943 all observed the finding of unilateral right adrenal hemorrhage in their respective reports.

4. *Adrenal Hemorrhage in Meningococcic Infection without Clinical Waterhouse-Friderichsen Syndrome:* In 1948, Daniels[10] in the same review of three hundred autopsy cases of meningococcic infection, found five out of one hundred and twenty-six cases with adrenal hemorrhage which did not present the clinicial picture of the Waterhouse-Friderichsen syndrome.

5. *Clinical Waterhouse-Friderichsen Syndrome which Ended in Recoveries:* These, recent investigators prefer to call fulminating meningococ-

cic septicemia. We might also call it arrested Waterhouse-Friderichsen Syndrome. A review of the literature up to this time (December, 1953) revealed about thirty recovered cases since the use of the sulfa drugs. Magnuson[24] in 1934 was the first to state that he saw a case of recovery from the Waterhouse-Friderichsen syndrome, but he gave no details. Carey[8] in 1940 reported the first recovered case observed in a 27 year old woman in 1937. D'Agati and Marangoni[9] who in their previous report discounted the possibilities of recovery, changed their stand in 1945 when they observed one themselves and offered the explanation that they now "believe that the bacteremia, toxemia and adrenal hemorrhage are quantitative and, therefore, this triad with its train of pathological changes may be mild to moderate and fully compatible with recovery."

### ETIOLOGY

In 1894, Voelker[38] and in 1898, Andrews[2] incriminated smallpox when they thought that the skin lesions simulated the smallpox lesions, but this was later disproved when the Waterhouse-Friderichsen syndrome did not occur during the smallpox epidemic. Staphylococcus aureus and albus were isolated by Dudgeon[12] in one case in 1901 and by Rucks and Hobson[33] in another case in 1943. However, the clinical history of the former was not typical of the syndrome while the latter concluded that it was a contaminant since subsequent examinations were all negative and thereby treated the case as a meningococcus infection. The Streptococcus was indicted by Little[23] when he found cocci arranged in clumps and in threads inside the blood vessels of the skin of two cases examined. He saw no cocci in the tissues. The blood cultures, however, failed to grow any organism. Drysdale[11] and Dudgeon[12] isolated the pneumococcus, an organism also capable of producing purpura as demonstrated by Julianelle and Reimann[19] in their animal experiments. Andrews[2a] in 1906 was the first to isolate the meningococcus in a blood culture and also to demonstrate it in a blood film as "exclusively intracellular coccus, in pairs or groups of half a dozen" in the polymorphonuclears. With Gram's stain it proved to be a Gram negative diplococcus. However, it was not until the 1914–1916 epidemic that the definite association of the Waterhouse-Friderichsen Syndrome with the meningococcus was recognized when McLagan and Cooke[25] isolated the organism and proved it the causative agent of the syndrome. Since then many reports have been made to this effect. Netter and Salanier[29] in 1916 were one of the first to demonstrate the meingococcus in the purpuric smears. In 1941, Lindsay, Rice, et al[22] isolated *H. influenza* in 2 out of 8 cases of Waterhouse-Friderichsen Syndrome.

Other organisms isolated or found associated with the disease entity are

the colon bacillus, *B. pyocyaneus* and Friedlander's Bacillus. A fair number were negative or sterile such as those found by Friderichsen[14b], in 7 out of 12 cases and by Glanzmann[15a] when he cultured the heart and the spleen. The explanations offered by Bamatter[3] for the sterile cultures were: (A) Phagocytosis by body cells, (B) antibodies in the serum carried over into the culture media, and (C) the organisms may be few but essentially virulent in effect. In 1937, Sacks[34] found in a review of the cases that 60 per cent were attributable to the meningococcus and 40 per cent to various other organisms or were sterile. The present concensus of opinion among a number of investigators in the face of a varied number of isolated organisms is that the sole agent is the meningococcus and that the rest are either secondary invaders or contaminants as proven by the frequent finding of the meningococcus and the increased incidence of the Waterhouse-Friderichsen syndrome during a meningococcus epidemic. On the other hand, adrenal hemorrhages have been found also in scarlet fever, streptococcus meningitis, smallpox, diphtheria, pneumonia and anterior poliomyelitis.

### INCIDENCE

The incidence of the Waterhouse-Friderichsen Syndrome is 3.3 per cent of all meningococcus infections as observed by several investigators[10, 20, 40]. In 1934, Sacks[34] noted that 70 per cent occurred below two years of age and 90 per cent below nine years. However, in 1947, after World War II, 40 of 175 cases reported or 23 per cent occurred among adults[37]. Sex is not a factor[20]. Seasonal incidence shows a fastigum in winter and early spring, some in fall and a few in summer. About 30 recoveries have been reported so far. Other factors involved are epidemic, recognition, and reporting.

### PATHOGENESIS

There is general agreement that the meningococcus gets its initial foothold through the invasion of the nasopharynx, producing primary bacteremia and toxemia with resultant overwhelming of the primary hematogenous defenses and causing severe damage to the vascular system, as evidenced by medical shock and hemorrhages into the skin, adrenals, mucosa and serosa. Also most observers agree that the medical shock is directly responsible for death and that it is due to either, or both, adrenal insufficiency and generalized tissue changes secondary to septicemia. It is believed that adrenal insufficiency leads to exhaustion of the hormonal supply and that a generalized peripheral vascular dilatation which may signify loss of vasopressor function of the adrenal cortex results in a feeble pulse, low blood pressure and cyanosis. Direct bacterial invasion of the endothelial lining of the capillaries as proven by Hill and Kinney[17] with resultant severe damage to the peripheral vascular bed may also be a strong contributing factor to the production of shock.

Hemorrhages into the skin have been proven to occur in the same manner and the same mechanism most likely is involved in the occurrence of hemorrhage into the adrenal glands. Invasion of the capillary endothelial cells results in edema and inflammation followed by necrosis and consequent hemorrhagic extravasation. Involvement of both the skin and adrenals support the theory of ectodermal tropism of the meningococcus since both tissue elements come from the same ectodermal anlage. Conversely, the same theory is offered as the explanation for the common site of the hemorrhage.

Shock, if survived, disappears within 6 to 8 hours and is followed by a second critical period as observed by D'Agoti and Marangoni[9] in two cases which survived shock only to die later from hepato-renal failure.

The lymphatic constitution, often mentioned by early investigators as a factor in the pathogenesis of the Waterhouse-Friderichsen Syndrome, has been regarded more recently as probably a purely coincidental finding.

Banks and McCartney[5a] described an encephalitic group of cases which they explained are secondary to toxemia and anoxemia during the shock phase of the disease.

Selye[35] in his experiments, exposed animals to serious forms of stress and produced necrotic injuries in the adrenal glands. Bjorkland[6] believes that similar changes which may therefore occur in man due to excessive stimulation of the adrenal cortex results in a maximal function which can be maintained only for a short time. He believes that if treatment fails and the disease runs its course for some time, the adrenals begin to fail, show signs of exhaustion, and secondary hemorrhages occur. The length of time the adrenals can hold their own will probably vary individually and if hemorrhages intervene, the phase most likely becomes irreversible. A few indirect signs of augmented adrenal function according to Bjorkland[6] are increased white blood cell count with a shift to the left and lymphopenia, low serum albumin as found in Cushings syndrome, and a high blood sugar which is occasionally seen during treatment with ACTH. Hypoglycemia would signify exhaustion of adrenal function.

### CLINICAL MANIFESTATIONS AND LABORATORY FINDINGS

The clinical picture usually is ushered in by an upper respiratory infection in the midst of which the individual suddenly complains of one or several of the more common symptoms such as muscular or joint pains, headache, vomiting, chills and fever. A petechial or purpuric rash is almost always present and once it appears, increases in size and number with great rapidity to involve the various parts of the body including the conjunctiva and buccal mucosa. The patient quickly goes into delirium with confusion or restlessness and becomes irrational or by-passes this stage of excitement and suddenly lapses into stupor and coma. Convulsions have been observed in 21

per cent and cyanosis, in 46 per cent of cases. Some authors noted a similarity of the purpuric rash on the dependent parts of the body with postmortem lividity. Within a short time the patient goes into shock characterized by rapid, shallow and later terminal irregular respirations, a rapid, imperceptible pulse, and a low or unobtainable blood pressure. Anuria or oliguria and dehydration is a characteristic finding.

The lungs are usually clear and resonant although many times the breath sounds are harsh or a few coarse rhonchi are heard. Neurologically, the findings are variable although usually they are negative. The temperature varies from subnormal to 109°F.

Less common findings include low surface temperature with a high rectal temperature, muscle flaccidity, tremors, cough, edema of the lower extremities, strabismus, rigidity of the abdominal muscles and diarrhea.

The laboratory findings include a leucocytosis with a shift to the left and in a majority of cases toxic granulations are seen. Sometimes, at the earliest stages, the white blood cell counts are normal and this increases only when the patient lives long enough for a repeat count after 12–24 hours. The hematocrit is usually normal and there is no evidence so far observed of hemoconcentration to which shock could be attributed.

The eosinophile count is considered by recent observers as a fairly good guide to the status of the adrenals and as an aid in the duration of therapy with cortical hormones. A serial count has been recommended every one to two hours during the critical period. The eosinophile count has been observed to decrease in stress and increase in convalescence. Under extreme stress, it could be expected to be zero and if found to be above fifty, adrenal insufficiency or its onset should be suspected.

The Thorn test has been used to check on the adrenal status during convalescence. Where some residual adrenal damage due to hemorrhage has occurred in a recovered case, in addition to a Thorn test, X-ray of the abdomen may reveal some findings at the site of the adrenals if some parts of it have become calcified. Snelling and Erb[81] found eight cases in infants and children who had hemorrhage into the adrenals to have secondary calcification. Two of these showed up on X-ray during life.

The blood culture is positive in the majority of cases for *Neisseria intracellularis*. The spinal fluid is usually clear or occasionally cloudy; the smear and culture is variable. McLean and Caffey in 1931 found the petechial smear positive in 83 per cent of 18 cases and therefore recommended it as a quick method of bacteriological diagnosis especially in those cases where a rapid diagnosis is imperative. The technique originally described is simple and differs only from the ordinary blood smear in that the skin puncture is done at the site of a purpuric lesion.

The blood chemistries reported so far have been few and inconsistent as

noted by Bjorklund[6]. The potassium, $CO_2$ and chlorides are either decreased or normal, glucose and sodium diminished, normal, or increased, while the NPN and creatinine are increased or normal. Other chemistries reported included 4 plus cephalin flocculation and increased icterus index[35a], diminished total protein particularly the albumin fraction[13a], and decreased total cholesterol and cholesterol esters[35a]. Nor can a definite prognosis be deduced alone from the chemistry values obtained as evidenced by the two cases reported by D'Agati and Marangoni[9] both of whom had sodium retention; one died while the other recovered. An initial hyperglycemia has been explained by a hyperfunctioning adrenal, and hypoglycemia by an exhausted gland. It is generally agreed that in so far as the blood chemistries are concerned, if adrenal function is impaired, electrolyte changes might be expected. However, since the condition is hyperacute, changes may not have time to take place and normal findings may be obtained. That a prolonged acute phase with a long survival period will show more changes is a logical deduction.

Some of the complications observed among the cases that recovered are the following: 1) sloughing and ulceration of the ecchymotic areas, 2) gangrene of the extremities leading to bilateral amputation of both legs below the knees, 3) temporary stiffness of the involved knee joints, 4) temporary and slight impairment of hearing, 5) mild myopia, 6) hydrarthrosis of the knees and elbows, 7) temporary exhaustion, delirium with depression and with auditory and visual hallucinations, 8) temporary asthenia, 9) left corneal ulcer with ectopian and loss of lashes, 10) involvement of the ulnar nerves with resulting hyperesthesia, anesthesia and paralysis of the affected areas, 11) temporary generalized edema and, 12) urticaria, due to a delayed reaction to antitoxin administration.

## DISCUSSION

Discussion will be limited to a comparison between the two cases presented.

Clinically the two cases were indistinguishable, and both presented the typical picture of the Waterhouse-Friderichsen syndrome. Each had a sudden onset and case 2 was preceded by an upper respiratory infection. The occurrence of pain in the leg, a high fever with or without convulsions, and vomiting at the onset of a severe infection such as occurred in these two cases are characteristic findings. Purpura, restlessness, delirium and/or coma with difficult breathing, and a rapid pulse followed by shock with a low or unobtainable blood pressure, and an imperceptible pulse, occur in such quick succession that heroic therapy and continuous watchfulness are imperative.

Both cases were seen within a week's interval of one another. Initial

therapy instituted in both cases was similar since their sizes and ages were about the same. In both cases, the infection was unquestionably fulminating but the second case was even more so and is evidenced by several factors. (1) Only toxic granulations were seen in the blood film of case 1 while many Gram-negative intracellular diplococci were found in the blood smear of case 2 in addition to the toxic granulations; (2) both cases presented a generalized purpuric eruption. Those of case 1 were coalescent to a much lesser extent that those of case 2, where whole surface areas of the face and of both upper and lower extremities were involved with very little normal skin in between. The ecchymotic areas on the posterior surfaces of the extremities and on the back could be compared with post mortem lividity; (3) while case 1 was admitted in a state of shock, we were able to relieve the blood pressure in a fairly reasonable time after institution of therapy, while the onset of shock in case 2 occurred one hour after admission and in spite of the institution of continuous vigorous therapy it could not be alleviated.

This transformation into a state of irreversible shock in case 2 probably marked the onset of acute adrenal insufficiency secondary to massive adrenal hemorrhages as shown at autopsy. While case 1 received treatment 18 hours after the onset of illness and 4 hours after the onset of purpura, case 2 received similar treatment within 8–9 hours after the onset of illness or ½ hour after the onset of purpura and yet the latter ended fatally while the former recovered.

It cannot be determined whether the patient who recovered had adrenal hemorrhage or not, although it seems safe to assume that whatever adrenal damage, if any, had occurred most probably was reversible.

Up to one year after his discharge, case 1 has had no complaints referable to the adrenals. Added to this is the normal Thorn test just prior to discharge plus the normal blood chemistries obtained 9 months after discharge.

Case 1, admitted in a state of shock and with generalized purpura, was recognized as a fulminating meningococemia and thereby received prompt therapy which proved successful. Case 2 was admitted in a post-convulsive state with hyperpyrexia and delirium without purpura. While the diagnosis was obvious in the first case, it was not so obvious in the second. The meningococcus as an etiologic agent in case 2 was not suspected until about three hours after admission when a routine white cell and differential count revealed toxic granulations and intracellular diplococci. This led to a more thorough search for purpura which resulted in the finding of 2 "suspicious petechiae" at about the level of the left iliac crest. Within the next half hour the purpuric lesions had increased from 2 "suspicious petechiae" to a generalized and extensive hemorrhagic phenomenon which involved the whole face, neck, body and extremities. Vigorous therapy was instituted as

in case 1, however, this time to no avail. Death occurred 3½ hours after the onset of purpura or 2 hours after the onset of shock. Bush and Bailey[7] stated that, "The alarming rapidity with which this condition progresses to a fatal termination, if untreated, makes it imperative to institute appropriate therapy with the least possible delay." It is therefore worth while to bear in mind, particularly during winter and spring, the possibility of the occurrence of fulminating meningococcic septicemia in the absence of a tell-tale purpuric eruption in an obviously severe, sudden and acute, but obscure infection.

The value of the eosinophile count as a guide to adrenal status has been indicated in these two cases. It is interesting to note that the initial eosinophile counts in both cases were 40 per cu. mm. suggesting exhausted adrenal glands.

The blood chemistry results in case 1 demonstrates their limited value in an acute condition like the Waterhouse-Friderichsen syndrome.

The therapy used in these cases was specifically directed against the meningococcus and also included supportive treatment of the adrenals, respiratory and cardiovascular systems.

From the public health standpoint, throat cultures done on the members of the family of case 2 revealed a positive culture from the mother for the same type of meningococcus. All members of the family were therefore prophylactically treated with sulfadiazine.

## DISCUSSION

Dr. Sidney Ross

The following regime has been adopted at Children's Hospital for the management of patients with Waterhouse-Friderichsen syndrome.

1. Laboratory work-up
   - A. Spinal tap
     - (1) Stat on admission
     - (2) Daily thereafter for 3 days if positive; then every 3rd day until discharge.
     - (3) At least one repeat tap if negative
   - B. Blood Culture
     - (1) Stat on admission
     - (2) Daily thereafter for three days
   - C. Nasopharyngeal Culture
     Stat on admission
   - D. Petechial Smear
     Stat on admission
   - E. Blood Chemistries
     - (1) Bun, blood sugar, $CO_2$, chlorides, sodium and potassium
     - (2) Stat on admission and daily thereafter for 3 days

F. Hematocrit
Stat on admission
G. CBC and Urine
(1) Stat on admission
(2) Daily thereafter for 3 days until discharge
H. Total Circulation Eosinophil Count
(1) Stat on admission
(2) Every 2 hours for the first 12 hours
(3) Then every two days
I. Thorne Test (with ACTH)—5th, 10th and 15th day
J. EKG Daily as Indicated
K. Blood Sulfa Level Daily

2. Clinical Observations
A. Temperature, pulse, and respiration every two hours during the first 12 hours, then every 4 hours thereafter.
B. Blood Pressure
(1) Every hour during the first 12 or 24 hours as indicated
(2) Then every 2 hours during the next 24 hours as indicated
(3) Then every 4 hours as long as necessary
C. Observe for congestive failure
(1) Enlargement of the liver
(2) Dyspnea
(3) Heart rate
(4) Rales at lung bases
(5) X-ray of the heart, portable
(6) Edema

3. Treatment
A. Continuous oxygen
B. Continous IV stat on admission
(1) Blood transfusion stat
(2) Adequate amounts of saline
(3) Glucose with Hartmann's solution
C. Antibiotic therapy
(1) Aureomycin IV 10 mgm/kgm every 8 hours
(2) Sodium sulfadiazine IV 100 mgm/kgm every 8 hours
(3) Penicillin (aqueous, crystalline) 1,000,000 u. stat IM every two hours.
D. Cortisone
(1) 50 mgm stat IV and 50 mgms stat IM
(2) Then 25 mgm IM every 12 hours for 2 days
(3) Then 25 mgm orally every 12 hours for 2 days.

## BIBLIOGRAPHY


1. Aegerter, E. E.: The WFS, A Review of the Literature and a Report of 2 cases. JAMA **106:** 1715–19, May 16, 1936.
2. Andrews, F. W.: Transactions, Path. Society of London 1898, p. 259.
2a. Andrews, F. W.: A Case of Acute Meningococcal Septicemia, Lancet T: 1172, 1906.
3. Bamatter: Quoted by Sacks.
4. Batten, F. E.: Transactions, Pathological Society of London, 1898, p. 258.
5. Banks, H. S. and McCartney, J. E.: Meningococcal Adrenal Syndromes and Lesions, Lancet 1943 T: 771.
5. Banks, H. S. and McCartney, J. E.: Meningococcal Encephalitis, Lancet 1942 T: 219.
6. Bjorklund, S. I.: The Waterhouse—Friderickson Syndrome: Acta Pediatrica.
7. Bush, F. W. and Bailey, F. R.: The Treatment of Meningococcus injections with Esp. Reference to the WFS: Annals of Internal Medicine 1944, *XX*: 619.
8. Carey, T. N.: Adrenal Hemorrhage with Purpura and Septicemia (WFS) with Recovery; Case Report. Annals of Internal Medicine Vol. **13:** 1740, 1940.
9. D'Agati, V. C. and B. A. Marangoni: The Waterhouse—Friderickson Syndrome; New England Jr. of Medicine, Vol. **232:** 1, 1945.
10. Daniels, W. B.: Meningococcic Bacteremia; Arch. Int. Med. Vol. **81:** 145, 1948.
11. Drysdale: Quoted by Sacks.
12. Dudgeon, L. S.: The Etiology, Pathology and Diagnosis of Adrenal Hemorrhage. American Jr. Med. Sciences, **127:** 134, 1904.
13. Faloon, W. W., Reynolds, R. W., and Beebe, R. T.: The Use of the Direct Eosinophile Count in the Diagnosis and Treatment of WFS. New England Jr. Med. Vol. 242 No. 12.
14. Fridericksen: Quoted by Aegerter.
14b. Fridericksen: Quoted by Sacks.
15. Glanzmann: Quoted by Banks and McCartney.
15b. Quoted by Leirnson.
16. Grubschmidt, H. A., Graham, G. C., and Jessup, E. C.: A Case of Fulm. Meningococcemia Exhibiting the WFS and Demonstrating the Value of Cortical Extract Administration. Annals Int. Med. Vol. **26:** 1947.
17. Hill, W. R. and Kinney, T. D.: Cutaneous Lesions, Clinical and Pathological Study. JAMA **134:** 513, 1947.
18. Jacobi, M. and Harris, L.: Fulminating Purpuric Meningococcemia (WFS) with Recovery. Annals Int. Med. **22:** 876, 1945.
19. Jubianelle, L. A. and Reimann, H. A.: The Production of Purpura by Derivatives of Pneumococcus. Jr. Expt. Med. **43:** 87, 1926.
20. Kinsman, J. M., D'Alonzo, A. and Russi, S.: Fulminating Meningococci Septicemia Associated with Adrenal Lesions. Arch. Int. Med. **78:** 139, 1946.
21. Levinson, S.: The WFS Report of a Case with Autopsy Findings. Jr. Pediatrics **14:** 506, 1939.
22. Lindsay, Rice, C.; Et al: Waterhouse Fridericksen Syndrome. American Jr. Med. Science. **201:** 263, 1941.
23. Little, E. Graham: Cases of Purpura, Ending Fatally, Associated with Hemorrhage into the Supraenal Capsules. British Jr. Dermatology, 1901 XII: 445.
24. Magnusson, J. H.: Contribution to the Knowledge of Acute Suparenal Insufficiency in Children. Acta Pediatrica **15:** 396, 1934.

25. McLagan, P. W., and Croke, W. W.: Fulminating Type of Cerebro-Spinal Fever: Pathology and Cause of Death. Lancet TT: 1054, 1916.
26. McLean, S. and Caffey, J.: Endemic Purpuric Meningococcus Bacteremia in Early Life, The Diagnostic Value of Smears from the Purpuric Lesions. Am. Jr. Diseases of Children **42:** 1053, 1931.
27. Nelson, J. and Goldstein, N.: Nature of the WFS. Report of a Case with Successful Treatment with Cortisone. JAMA **146:** 1193, 1951, July 28.
28. Newman, L. R.: Report of Cure Effected with Cortisone: JAMA **146:** 1229-30, 1951, July 28.
29. Netter, A. and Salanier, M. and Mme. Wolfrom: A New Case of Hyperacute Purpura without Cerebrospinal Meningitis: Recognition of its Meningococcal Nature during Life by Microscopical Examination. Brit. Jr. Children's Diseases, 1917, XIV: 104.
30. Peabody, S. D.: Purpura Fulminans (The WFS). New England Jr. Med. **229:** 934, December 1943.
31. Rabinowitz, M. A.: Adrenal Hemorrhage in Infancy (2 Cases), Am. Jr. Med. Sciences, **166:** 513, 1923.
32. Rich, A. R.: A Peculiar Type of Adrenal Cortical Damage Associated with Acute Infections, and its Possible Relation to Circulatory Collapse. Bull. Johns Hopkins Hospital **74:** 1, 1944.
33. Rucks, W. L. and Hobson, J. J.: Purpura Fulminans (WFS) Report of a Case with Recovery. Jr. Pediatrics **22:** 226, 1943.
34. Sacks, M. S.: Fulminating Septicemia Associated with Purpura and Bil. Adrenal Hge (WFS); Report of 2 Cases with Review of the Literature. Annals Int. Med. **10:** 1105, 1937.
35. Selye, H.: The General Adaptions Syndrome and the Disease of Adaption. Jr. Clinical Endocrinology **6:** 117, 1946.
36. Snelling, C. E. and Erb, I. H.: Hemorrhage and Subsequent Calcifications of the Suprarenal. Jr. Pediatrics **6:** 22, 1935.
37. Taylor, C. E., Surgeon, A. and Landry, V. E.: WFS: Recovery from Shock in Fatal Case. Annals Int. Med. Vol. **26:** 599–603, 1947.
38. Voelker, A. F.: Pathological Reports, Middlesex Hospital, London, 1894.
39. Waterhouse, R.: A Case of Suprarenal Apoplexy. Lancet T: 576, 1911.
40. Weinberg, L. and McGavack, T.: The WFS; Report of a Case with Recovery. New England Jr. Med. **232:** 95, January 1945.
41. Williams, H.: Meningococcal Infections in Infancy and Childhood. Med. Jr. Australia TT: 557, 1942.

## LISTERELLA MENINGITIS

Alberto Portero, M.D.
A. Despirito, M.D.

Because of the rarity of meningitis due to *Listerella monocytogenes*, the following case report is made. This is believed to be the second patient with Listerella meningitis treated with broad spectrum antibiotics.

CASE REPORT

The infant, a negro male, was first admitted to Children's Hospital on October 29, 1953, at two weeks of age because of fever and anorexia of twenty four hours duration. He was seen by a physician on the day of admission and referred to the Outpatient Clinic because of fever of unknown origin. Generalized twitchings and irritability had been observed on the day of admission.

Past history: The child was born at a local hospital following a full term normal pregnancy and spontaneous delivery, and weighed seven pounds, six ounces at birth. He was placed on a formula of evaporated milk and water and was apparently well until the present illness.

The family history was noncontributory. The mother and father are in good health and four siblings are alive and well. There is no history of familial diseases.

Physical examination on admission revealed a two week old, well-developed, well nourished, irritable baby who appeared to be acutely ill. The temperature was 102.6°. The anterior fontanelle was bulging. The right ear drum was mildly injected. The lungs were clear to percussion and auscultation and the heart was normal. The liver edge was firm and extended 2 cm. below the right costal margin. The umbilicus was dry and well-healed. The child cried when his neck was flexed, the Brudzinski and Kernig tests were positive and the tendon reflexes were hyperactive.

The spinal fluid obtained on admission was cloudy, with 400 leukocytes/cu mm. polymorphonuclears, 76 per cent; lymphocytes 24 per cent; protein 40 mg/100 ml; and sugar 24 mg. The organism grown from culture was reported as a diphtheroid.

The blood count on admission revealed 11,900 leukocytes with 46 per cent polymorphonuclears and 54 per cent lymphocytes and was otherwise normal. There were 10 eosinophiles per cu. mm. Diphtheroids were reported as being present in blood culture. Urinalysis was normal.

On admission the child received the routine meningitis therapy of aureomycin and chloromycetin intravenously, in dosage of 10 mgm/kg, every six hours of the former, and 20 mgm/kg every six hours of the latter. Supportive therapy was given as indicated. The temperature remained elevated to 104° for three days. A sub-dural tap was done on the third day after admission and five ml. of fluid was obtained from the right side and 2.5 ml. from the left side. The organism was reported sensitive to terramycin, chloromycetin, achromycin, streptomycin, and erythromycin. The spinal fluid obtained on October 9th, twelve days after admission, contained 28 mgm. of protein, 58 mgm. sugar. There were 16 leucocytes, with 14 per cent polymorphonuclear and 86 per cent lymphocytes. Child was discharged on November 11 after being afebrile for eight days.

On November 14, three days later, the patient was readmitted because of irritability and fever. The anterior fontanelle was found to be bulging, there was nuchal rigidity and hamstring spasm, but the child otherwise appeared to be well.

The spinal fluid obtained shortly after admission was slightly turbid, with 114 mg. protein, and 28 mg. sugar, the white blood cell count being 735 with 48 per cent polymorphonuclear leucocytes. Spinal fluid culture again was reported as showing diphtheroids. The blood contained 34,200 leucocytes with 64 per cent polymorphonuclears and 36 per cent lymphocytes. The blood culture contained diphtheroids and proteus vulgaris. Child was given aureomycin and chloromycetin for thirteen more days, a response was noted within 24 hours. The spinal fluid prior to discharge was normal. One week later the child returned to clinic for a spinal tap. He had been asymptomatic at home and was doing well. The fluid was clear and contained 113

leucocytes with 28 per cent polymorphonuclear and 77 per cent lymphocytes. Protein was 23 mgm. and sugar 45 mgm. He was readmitted for observation, physical examination being essentially negative. During the next 17 days, he again received aureomycin and chloromycetin and remained afebrile. Blood count was normal, he gained weight and appeared to be well.

Examinations made during a throat culture disclosed normal flora and the blood culture was sterile. Agglutinations with febrile antigens were negative. Repeated examinations of subdural fluid were negative. Chest x-ray and PPD #1½ were negative. The spinal fluid culture was submitted to the communicable disease center, U.S.P.H.S., Chamblee, Georgia, where the organism was identified as *Listerella monocytogenes*. On December 21st, the spinal fluid was normal and the patient was discharged. He was next seen on January 4, 1954 in the out-patient department. The spinal fluid at this time was normal. The child was seen again on January 18th, two and a half months following the onset of the illness and was found to be gaining weight and to be asymptomatic. The physical examination was normal.

## DISCUSSION

Listerella is a short, plump rod, which is quite pleomorphic depending on the medium used for culture. It is a Gram-positive, motile bacillus which has been classified as a diphtheroid on many occasions because its motility is exhibited only under certain circumstances.

Listerella was first submitted as a new species in 1924 by Maury, Webb and Swann[5]. Nyfeldt[6] in 1928 first found Listerella in man in a patient with infectious mononucleosis. In 1918 an organism was isolated from a soldier and was thought to be a diphtheroid. Subsequent studies 24 years later proved the organism to be *Listerella monocytogenes*. It is very likely that the organisms isolated from other patients with meningitis, as in this child, have been mistaken for diphtheroids and if studied more thoroughly might have been found to be due to Listerella.

Infections due to Listerella subsequently have been described throughout the world. Its mode of transmission is unknown, though most likely transplacental infection plays some part. Burn[1] reported two cases in which infants were born on the same day on an outside maternity service in the same city and who subsequently died within two weeks from this infection. Line and Cherry[4] in 1952 reported two babies who were born within two days of each other in the same hospital, one of whom died of this infection. Kaplan[3] reviewed the literature in 1933 and reported 23 cases of *Listerella monocytogenes* meningitis. Hadelman[2] in 1946 reported a patient with Listerella meningitis who responded to penicillin and a sulfanilamide. Other reports of cures using the latter drug have followed.

The first reported cure using broad spectra antibiotics was in 1952 when aureomycin was used. This patient is believed to represent the second reported case of *Listerella monocytogenes* to be treated with the broad spectrum antibiotics with recovery. The first patient to be treated by Lirre

and Cherry[4], died at the age of nine months as a result of hydrocephalus. In our patient a subdural effusion was found, but subsequent taps were dry. The infant responded to aureomycin and chloromycetin during two courses of treatment, despite a latent period in which there was no therapy. This indicates that treatment should be maintained for a longer period, at least until two spinal fluids are entirely normal, despite a good clinical response. The offending organism was shown to be developing resistance to aureomycin and chloromycetin in this patient.

SUMMARY

A case of recurring *Listerella monocytogenous* meningitis is reported with a case history and mode of therapy. This is believed to be the second patient to be treated with broad spectrum antibiotics to recover.

The desirability of continuing antibiotic therapy until two negative cultures can be obtained and the patient is clinically well is stressed.

BIBLIOGRAPHY

1. C. G. Burn: Clinical and Pathological Feature of Infections Caused by New Pathogen of Genii Listerella, Am. J. Path. **12:** 341–348, May 1936.
2. Kaplan, K. M.: Listerellosis, New England J. Med. **232:** 755–759, June 28, 1945.
3. Hadelman, N. I. et al: Listerella Meningitis, J. Ped., **28:** 210–213, Feb. 1946.
4. Lirre, F. G., Cherry, W. B.: Meningitis due to *Listerella Monocytogenous*, J.A.M.A. **148:** 361–369, February 1952.
5. Murray, E. G. D., Webb, R. A., and Swann, M. B. R.: Disease of Rabbits Characterized by a Hitherto Undescribed Bacillus. J. Path. and Bact. **29:** 407–439, 1925.
6. Nyfeldt, A.: Etiologie de la Mononucleose Infectieuse. Compt. Rend. Soc. de Biol. **101:** 39a–59c, 1929.
7. Schultz, E. W.: Listerella Infections, Stanford Med. Bull., 3: 135–151, Aug., 1945.

ADDENDUM

Two recent articles on Listerella meningitis treated with broad spectrum antibiotics have appeared in the literature:

1. Binder, M. A. et al.: Listeria Meningitis, Ann. Int. Med. 38: 1315, 1953.
2. Finegold, S. M. et al.: Listeria Monocytogenes Meningitis, Arch. Int. Med. 93: 515–527, Apr., 1954.

# DIABETIC ACIDOSIS

Milton Glatt, M.D.
John E. Cassidy, M.D.

The following case report and discussion are presented to illustrate a rather typical case of juvenile diabetes. The basic fundamentals of the pathologic physiology and therapeutic management of diabetes in childhood are presented.

## CASE REPORT

S. W., a 6 year old colored female, and a known diabetic, was readmitted to Children's Hospital on 6/14/53 because of deep, labored respirations, vomiting, weight loss, and polyuria. The patient's first admission to Children's Hospital was in October 1951, during an acute asthmatic attack. She apparently had been suffering from asthma since two years of age, with the attacks becoming progressively more frequent and more severe in nature. She responded promptly to therapy and after a hospital stay of three days, was discharged as improved, to be followed in the allergy clinic. The urine at this time was reported as normal. Following discharge from the hospital the patient was followed in the allergy clinic and was seen on several occasions in the medical clinic for respiratory infections.

She was admitted to the hospital for the second time on 2/16/53 with a large fluctuant abscess on the right labia majora, polyuria, and polydipsia. Physical examination revealed an odor of acetone on her breath; she was undernourished, and moderately dehydrated with a respiratory rate of 48 per minute. The urinalysis revealed a four plus sugar and a four plus acetone with no diacetic acid present. The $CO_2$ combining power was twelve volumes per cent, and the blood sugar was 420 milligrams per cent. The hemoglobin was 12 grams, and the white count was 18,400 with a slight shift to the left in the *Schilling index*. The child was treated with regular insulin, intravenous fluids, and penicillin. The abscess was incised and drained. Within five hours after admission, the $CO_2$ combining power was 43 volumes per cent. and after 24 hours the urine was free of acetone with a 2 plus sugar. The blood sugar was 150 milligrams per cent. The diabetes was regulated easily with an appropriate diet and 34 units of NPH insulin daily. At the time of discharge on 3/4/53 the patient's urine was negative for acetone and showed one plus sugar.

Following discharge from the hospital, the child did well until one week prior to the present hospitalization when she showed increasing glycosuria. Three days before admission a respiratory infection accompanied by cough and difficult respirations appeared. On the day of admission the patient vomited several times. The urinalysis at this time showed a four plus sugar and four plus acetone; the $CO_2$ combining power was 12 volumes per cent, and the blood sugar level was 450 milligrams per cent. The acidosis was corrected with regular insulin and intravenous fluids, and the patient was placed on a diet of 180 grams of carbohydrate, 80 grams of protein and 80 grams of fat. Depending on what the fractional urinalysis showed throughout the day, NPH and regular insulin were administered. In spite of gradually increasing the NPH insulin to 60 units daily, the urine continued to show a three plus sugar, while the blood sugar level remained at about 350 milligrams per cent with some diurnal variation. The daily requirement of insulin reached levels as high as 66 units of NPH, together with 15 units of regular insulin without completely controlling the

glycosuria or the glycemia. The respiratory infection was treated with aureomycin with some improvement and leveling off of the insulin requirements at 60 units of NPH insulin daily. In the interim a bout of asthma complicated the clinical course. Upon recovery from this episode the insulin requirement was re-established at 60 units of NPH insulin daily and the patient was discharged with a one to two plus sugar in her urine and a blood sugar level of 150 milligrams per cent. She has been seen regularly in the diabetic clinic and at the present time is doing well.

## DISCUSSION

The patient illustrates many of the features of juvenile diabetes. The diagnosis was established during a bout of severe acidosis associated with an infection. She was regulated satisfactorily on a measured diet and a single daily dose of NPH insulin. Her progress was good until she developed a respiratory infection associated again with severe acidoses. Re-establishment of control of the diabetes was more difficult and required larger doses of insulin because of the persistence of the infection.

Aside from the degenerative changes which occur later, acidosis is the most serious complication in the life of a diabetic. Our constant goal in the management of these patients is that states of severe acidosis and coma shall never develop. This requires education of the patient and parents in detecting the early signs of impending trouble and the prompt reporting of these to the physician. Extra doses of insulin administered early will usually prevent the development of severe acidosis, if the underlying factors are detected and corrected at the same time.

Diabetic or ketonemic acidosis is due primarily to insulin deficiency and this may be caused by one or a combination of several of the following factors:

A. Omission of insulin
B. Failure to increase the dose of insulin in the presence of infection.
C. Carelessness in regulating the amount of insulin required.
D. Dietary indiscretion
E. Acidosis and, or, coma may be the initial episode leading to the discovery of the disease in an individual.

The principal metabolic disturbances which occur as a result of the insulin deficiency are the following:

A. *Hyperglycemia*—This results from decreased glycogenesis and increased glycogenolysis and to a lesser degree from inability of the tissues to utilize glucose. The resulting glycosuria is associated with increased renal water loss.

B. *Ketosis*—In the presence of impaired utilization of glucose, fat metabolism is increased with the subsequent overproduction of ketone bodies in the liver. With the development of acidosis, further impairment of carbohydrate metabolism occurs, increasing hyperglycemia, glycosuria

and polyuria. As dehydration increases, renal function is impaired and the ketonemia increases. The degree of ketonemia, in combination with the acidosis which develops, is probably responsible primarily for the cerebral narcosis which is present.

C. *Metabolic acidosis*—Lowering of the blood pH and diminished alkaline reserve in the body fluids result from the accumulation of ketone bodies and the loss of mineral cations excreted with them. Determinations of blood pH and carbon dioxide combining power are necessary for proper evaluation of this phase of the metabolic disturbance. Other changes occur which are strongly influenced by the acidosis, e.g., diminished oxygen exchange in the tissues, interference with the enzyme systems of the body, inhibition of insulin action, and increased tissue catabolism. The last is accompanied by a loss from the cells of potassium and phosphorous which are then excreted by the kidneys. As long as the urinary output is adequate, plasma levels of potassium may be normal, but when renal failure develops the plasma concentration may rise, even though there is a total tissue deficit. As the acidosis is corrected, there is a return to the cells of the potassium from the plasma and this may be rapid enough to produce an actual plasma depletion. The resultant hypokalemia may produce the clinical picture of respiratory paralysis and weakness. Characteristic cardiac involvement in hypokalemia may be demonstrated on the electrocardiogram.

D. *Dehydration*—results from excessive water loss via the kidneys accompanied by the excretion of electrolytes, glucose and ketone bodies. There is also present an increased insensible loss of water through the lungs and skin because of dehydration.

E. *Coma*—is the clinical manifestation of the progression of all of these changes to an advanced stage. Death follows unless steps are taken to interrupt and correct the metabolic changes.

### *Treatment*

In mild early cases of acidosis in known diabetics, the administration of extra amounts of insulin and the correction or elimination of the underlying cause will be adequate. In patients with severe acidosis, dehydration, and coma more vigorous measures are necessary.

The two most important phases of treatment are supplying adequate insulin and combating dehydration by adequate fluids and electrolytes. There is no precise rule which automatically determines the proper dose of insulin. The age of the patient, the severity and duration of the acidosis and subsequent amounts will depend on the response as shown by blood sugar levels and the $CO_2$ combining power, together with urine sugar and acetone determination.

Parenteral fluid therapy is aimed first at repairing the extracellular fluid. This can be accomplished by the use of Ringer's solution, Ringer-lactate, ⅙ M lactate, glucose solution, and potassium chloride. To correct acidosis quickly 1.4% sodium bicarbonate or ⅙ molar sodium lactate is given. We prefer the latter, using the formula (40-patients $CO_2$ combining power × 1.8 × patients weight in kilograms = amount of ⅙ molar sodium lactate to be administered. The aim is to raise the $CO_2$ combining power to between 30 and 35 volumes % so as to avoid overcorrection and the possible production of alkalosis.

In the postacidotic phase, the need for intracellular electrolytes, principally potassium arises. If potassium salts are given too early in the treatment, especially in the presence of renal impairment, there is a real danger of producing hyperpotassemia. The use of electrocardiogram and serum potassium level determinations by the flame photometer can afford guidance along this line.

When persistent circulatory collapse is present, transfusions of plasma or whole blood will be of benefit.

Intravenous fluids must be administered until fluids are taken readily by mouth.

A most important phase of the treatment consists in the elimination of an infection which is usually present in juvenile diabetics and precipitates the crisis.

*the new basic concept in infant feeding...*

# Lactum

## MEAD'S LIQUID FORMULA FOR INFANTS


Conforming in every respect to the latest and most scientific evidence on infant feeding, Lactum provides a clinically proved cow's milk formula, with demonstrated nutritional advantages, plus new convenience made possible by its ready-to-use liquid form.

Outstanding among Lactum's nutritional benefits is its generous milk protein content—providing a more-than-ample margin of safety above the Recommended Daily Allowance. Its natural milk fat not only supplies an effectively utilized source of calories but permits a uniformly smooth, perfectly homogenized formula. Supplementary carbohydrate (Dextri-Maltose) is incorporated for caloric adequacy and protein sparing.

Both in formulation and in manufacture, Lactum reflects Mead Johnson and Company's long experience in developing more effective products for infant feeding to meet the changing needs of the medical profession.

Lactum's time-saving convenience is welcomed by today's busy young mothers. They merely add 1 part Lactum to 1 part water for a formula supplying 20 calories per fluid ounce.

MEAD JOHNSON & COMPANY • EVANSVILLE, INDIANA, U.S.A.

MEAD, JOHNSON & COMPANY, Suite 419 Eig Building, 8641 Coleville Road, Silver Spring, Maryland. JU 9-1222